7. MALFORMATIONS OF THE GUT (E1-E4)

Subdivisions of malformations of the gut and associated structures and organs are inevitably rather arbitrary. For example, it would be difficult to defend the inclusion of exomphalos (E4), or at least all cases, but it is convenient to include them.

TRACHEO-OESOPHAGEAL FISTULAE AND OESOPHAGEAL STENOSES (E1)

The varying anatomical defects resulting in atresias of the oesophagus and tracheo-oesophageal fistulae have been classified in various ways, but the present records are with few exceptions insufficiently detailed for use of any such classifications. Most of these defects involve some degree of incomplete separation of the oesophagus and trachea during the fourth and fifth weeks of embryonic life and asynchrony or other disorder of development mostly affecting the oesophagus. The result may be a tracheo-oesophageal opening and/or a failure of the oesophageal tube to join up with the upper end of the foregut which will form the stomach. Alternatively, simple atresia of the oesophagus may result from failure of the lower part of the oesophageal tube to recanalize. In view of this variation of embryogenesis it is difficult to know how far to expect homogeneity or heterogeneity of etiological factors for the different types.

Frequency and mortality

Medical interest in tracheo-oesophageal fistulae and oesophageal stenoses has steadily increased as diagnosis and surgical repair techniques have improved, and there is now a large literature on the subject. However, perhaps because of the low frequency, few birth series have been reported, and most numerical information comes from series of cases referred to surgeons.

As will be seen from Table 7.1, the over-all frequency of the condition in all single births in the study centres is about 1 in 10 000, and no cases were reported in nine centres which contributed over one-third of all single births. Of the 45 cases, 3 infants were stillborn, 24 died and 18 left hospital alive. So that of 406 604 single liveborn children 24, or 0.06 per 1000 total births, died of tracheo-oesophageal fistula, etc. This may be compared with deaths from this cause alone of about 0.15 per 1000 total births in the British Perinatal Mortality Survey (Butler & Bonham, 1963), but the latter figure includes children in whom there were other malformations.

It will be seen from Table 7.2 that there were 15 infants (including 4 stillbirths and 5 who died in hospital) in the multiple or N group who had tracheo-oesophageal fistula or atresia. In all, the mean frequency of the condition in this series appears low relative to estimates from elsewhere. It seems inevitable, in view of the very short period for which mothers in many centres in this study were kept in hospital after confinement, that those recorded were not all that occurred. The highest total frequency was in the Royal Women's Hospital, Melbourne, where there were three cases grouped as E1 and five in the multiple (N) group—a total frequency of about 1 per 1000. Yet curiously enough there were no cases in Melbourne 2, the Queen Victoria Hospital, where selection for admission is very similar.

Even if there was not the additional uncertainty involved in comparison of the data because of selective admission of these cases to hospital by reason of the very high frequency of association with hydramnios, it is impossible to know whether there are real regional frequency differences.

Sex proportions (M/M+F)

Of the 45 cases in E1, 27 were males, and of the 15 cases where there were other malformations 9 were males, a total sex proportion of 36/60 = 0.60. Such a male excess has been described in several series of cases.

Taking the two groups together, the picture of sex and mortality is as follows:

	Males *		*Females* *		*Sex proportion*
Left hospital alive	20 (5)		4 (1)		0.83
Died in hospital	15 (3)	16 (4)	14 (2)	20 (5)	0.52
Stillborn	1 (1)		6 (3)		0.14
Total	36 (9)		24 (6)		0.60
Mortality %	44.4		83.3		

* The figures in parentheses are the cases in the N group and are *included* in the preceding figure.

From this table it would appear that there is a higher frequency in males but a suggestion of a

higher mortality in females. Unfortunately, there is often failure to state the sex of cases in several large series described by surgeons (e.g., Holder et al., 1964) so that whether this phenomenon has been observed elsewhere cannot be determined.

Associated malformations

It will be seen from Table 7.2 that 15 of the total of 60 cases of tracheo-oesophageal anomaly (25%) were in the N group. Seven had one type of anal atresia, three had renal malformations, two had cleft palate and three had interventricular septal defects. The pattern is in accord with the distribution of malformations described by Holder et al. (1964) but in that " surgical " series more associated malformations were discovered (54%). It has to be remembered, however, that all cases in that series were fully investigated and they either had an operation or came to autopsy.

Tracheo-oesophageal fistula in twins

In two MM pairs and one FF pair, one twin was affected and the other was normal. None were affected in MF pairs.

ANAL ATRESIA (E2)

It is impossible, from most of the recorded descriptions in this study, to distinguish between a number of different defects which result in the absence of a patent opening to a normal rectum; (*a*) there may be failure of development of any proctodaeum and the gut therefore ends blindly; (*b*) there may be failure of disappearance of the membrane which for a time separates the proctodaeum from the lower end of the gut—perhaps most usually called imperforate anus; (*c*) the lower end of the gut does not meet the proctodaeum or is not canalized but represented by a fibrous band. It appears to be most frequently in this last group (*c*) that there are recto-vesical, recto-urethral, recto-peroneal and recto-vaginal fistulae. It is not possible from the descriptions of the reported defects to classify cases in accordance with such a rough grouping or with the classifications suggested either by Ladd & Gross (1934) or by Browne (1955). Indeed, even with much better descriptions, it is unlikely that any really satisfactory grouping or at least one universally acceptable could have been found. There is still much difference of opinion as to the morphological situation and the embryogenesis of these conditions. All represent end-results of failure of differentiation at specific stages of the common cloaca present in the earlier embryo. It is not surprising, therefore, that some cases are associated with other malformations of the urogenital tract. In short, we might expect considerable etiological heterogeneity in different types of cases and perhaps, in particular, differences in cases without fistulae and those with fistulae and/or anomalies of the genitalia.

Types and frequencies of anal atresia when the only recorded defect

The data are set out in Table 7.1. It will be seen that all cases with and without fistulae but no other malformations have an over-all frequency of about 0.17 per 1000 total single births. The numbers are so few in different countries that division by types is reasonable only for grouped cases. In so far as the individual cards allow of distinction, the various types were: " imperforate anus ", 48; " recto-vaginal fistula ", 8; " ano-peroneal fistula ", 8; " anal or rectal atresia ", 6; and " ano-scrotal fistula ", 2. No cases were described by the currently fashionable term " ectopic anus ".

Anal atresia occurring with other malformations and classified in the N group

In all there were 38 cases where anal atresia of one type was one of several malformations in the same child (27 males, 8 females and 3 of indeterminate sex). The seven cases associated with tracheo-oesophageal fistula appear in Table 7.2 and the three cases associated with exomphalos in Table 7.4. The remaining 28 cases are listed in Table 7.3.

It is difficult to be consistent in grouping many of the cases, mainly because " intersex " conditions of the external genitalia and failure of differentiation of the primitive cloaca make it particularly difficult in many cases in the N group to assign to arbitrary groupings under " gut " or " urogenital system ". However, the full descriptions recorded by the clinicians are available to readers who are interested. Eleven of the cases are clearly " mixed ", there being some associated defect of the urogenital tract.

Cases of sirenomelia have not been discussed in this chapter. Few, if any, of these cases have an anus or rectum.

Sex proportions in anal atresia

Of the cases in the E2 group the sex proportion (M/M+F) was 47/72, or 0.65. The male excess is, however, accounted for entirely by cases described simply as " imperforate anus ". Of the 38 cases in

the N group the sex proportion (M/M+F) was 28/35, or 0.80 (three cases were described as pseudo-hermaphrodites of indeterminate sex). Of the 28 males, 22 are described as having imperforate anus. It would seem, therefore, that there is a large male excess of cases and that possibly this is accounted for mainly by males where the lesion is simple failure of perforation of the anal membrane. Weinstein (1965) has recently reported two families where males had simple imperforate anus and the pattern of inheritance was compatible with a single sex-linked recessive gene hypothesis. Some of the male excess could be explained on such a basis. Against such a hypothesis, however, it should be noted that six of the cases called imperforate anus also had urogenital defects.

Anal atresia in twins

In one MM pair and in two FF pairs one twin was normal and the other had anal atresia. In one MF pair the female was affected and the male normal.

OTHER MALFORMATIONS OF THE GUT (E3)

This is a heterogeneous group in which, for convenience, have been included biliary duct atresia and abnormalities of pancreas. In Table 7.1, however, only gut stenoses are included. The numbers are small and they range from single to multiple stenoses and from duodenal-jejunal stenosis, a common site, to stenosis or absence of colon and rectum. The sex ratio in these cases, as may be noted from the table, is not noticeably disturbed.

As is well known, atresia of the gut frequently occurs in Down's syndrome, and in sirenomelia part or whole of the large gut is absent. Apart from these conditions atresia of the gut also occurred in seven cases in the N group.

EXOMPHALOS (E4)

A dividing line between umbilical hernia and exomphalos cannot always be drawn with certainty. In turn, exomphalos proved difficult to distinguish from failure of closure of the anterior abdominal wall or agenesis of the abdominal musculature. In part, these difficulties arise because there is some variability in use of the terms exomphalos or omphalocoele in different parts of the world. British medical dictionaries tend to equate the two terms and define each as indicating protrusion of the abdominal contents into the umbilical cord (essentially following failure of withdrawal of the developing gut from the cord). Elsewhere exomphalos appears to be used to indicate all massive extrusions of the abdominal contents whether into the cord or through a defective abdominal wall. In the Basic Tabulations by Centres booklet lists the terms used by those recording have been followed.

Frequencies of exomphalos (E4) as the only recorded malformation

In all there were 41 cases where exomphalos was the only condition or where any other associated malformation such as volvulus may be interpreted as a mechanical consequence of protrusion of the abdominal contents into the cord. This represents a frequency of about 1/10 000 of all single births. There was no indication, as would perhaps not in any event be detected from the small numbers, of any undue frequency in particular countries.

Exomphalos in cases in the N group

In 25 cases " exomphalos " was only one of two or more malformations. There was a considerable range of associated malformations. However, as will be seen from Table 7.4, in 12 cases the associated malformations were urogenital. There were also three cases where imperforate anus occurred—two, in association with genital hypoplasia and one not recorded as so associated (these cases are *not* included in Table 7.3).

In three cases harelip or harelip and cleft palate and in one cleft palate only were associated and there were three examples of talipes. There were also six cases of malformation of the extremities, and five cases of cardiac malformations.

In addition to these 25 cases where exomphalos occurs as one of multiple malformations, there were seven other cases where " agenesis of the abdominal wall ", " absence of abdominal musculature ", etc., was one of the malformations in cases in the N group. As noted in section 15, it is likely that a proportion of these cases are the result of homozygosity for a single recessive gene.

Sex proportions (M/M+F) in cases of exomphalos

In E4 there were 26 males and 15 females, a sex proportion of 0.63 (Table 7.1). In the cases in the N group there were 13 males and 9 females and 3 where the sex was indeterminate, a sex proportion of 0.59; and of the 7 cases with agenesis of abdominal wall, etc., 4 were males and 3 females. The over-all sex

proportion of all cases where this type of defect was present was 43/70, or 0.61.

Mortality

In exomphalos alone 19 of 41 cases were stillborn or died in hospital (46.3%) and in cases in the N group where exomphalos was one of the malformations 20 of 25 (80%) of cases failed to survive. In contrast to tracheo-oesophageal fistula, however, there is no apparent difference in mortality by sex.

Exomphalos in twins

There were only three cases of exomphalos in twins. One twin of each of one MM and two FF pairs had exemphalos and the other was normal.

SEX PROPORTIONS (M/M+F) IN THE E GROUP

As will be noted from the data in Table 7.1, more males than females were affected in each group and there were 120 males and 74 females, a sex proportion of 0.62. This proportion is significantly higher than for all single births ($P < 0.01$). In the 76 cases in the N group where sex was determinable and one or more E-group malformations occurred, there were 49 males, a sex proportion of 0.60.

TABLE 7.1
MALFORMATIONS OF THE GUT (E1-E4) IN SINGLE BIRTHS

CENTRE		Tracheo-oesophageal fistulae and stenoses (E 1)				Anal atresia (E 2)				Other gut malformations (Part of E 3)				Exomphalos (E 4)			
		Number of cases			Per 1000 total births	Number of cases			Per 1000 total births	Number of cases			Per 1000 total births	Number of cases			Per 1000 total births
		M	F	T		M	F	T		M	F	T		M	F	T	
I 1	MELBOURNE	2	1	3	0.38	0	0	0	-	1	1	2	0.25	2	1	3	0.38
I 2	MELBOURNE	0	0	0	-	0	1	1	0.26	2	1	3	0.76	0	0	0	-
II	SAO PAULO	5	2	7	0.49	1	2	3	0.21	2	0	2	0.14	2	0	2	0.14
III	SANTIAGO	0	1	1	0.04	1	0	1	0.04	1	1	2	0.08	1	1	2	0.08
IV 1	BOGOTA	0	0	0	-	4	1	5	0.27	0	0	0	-	1	0	1	0.05
IV 2	MEDELLIN	0	0	0	-	0	1	1	0.05	0	0	0	-	2	0	2	0.10
V	CZECHOSLOVAKIA	3	1	4	0.20	0	4	4	0.20	5	2	7	0.35	0	1	1	0.05
VI	ALEXANDRIA	1	0	1	0.10	1	0	1	0.10	0	0	0	-	1	1	2	0.21
VII	HONG KONG	0	0	0	-	0	1	1	0.10	0	2	2	0.20	1	1	2	0.20
VIII 1	BOMBAY	1	2	3	0.08	9	3	12	0.30	0	0	0	-	3	5	8	0.20
VIII 2	CALCUTTA	0	0	0	-	2	0	2	0.10	0	0	0	-	1	0	1	0.05
IX 1	KUALA LUMPUR	0	1	1	0.06	7	2	9	0.56	1	2	3	0.19	2	0	2	0.12
IX 2	SINGAPORE	0	0	0	-	4	2	6	0.15	0	0	0	-	3	0	3	0.07
X 1	MEXICO CITY	7	2	9	0.36	4	1	5	0.20	2	0	2	0.08	1	0	1	0.04
X 2	MEXICO CITY	0	0	0	-	3	1	4	0.28	0	0	0	-	0	0	0	-
XI	BELFAST	3	3	6	0.21	2	2	4	0.14	1	1	2	0.07	2	1	3	0.11
XII	PANAMA CITY	0	0	0	-	1	1	2	0.13	0	0	0	-	0	0	0	-
XIII	MANILA	0	1	1	0.03	1	1	2	0.07	3	1	4	0.13	1	1	2	0.07
XIV 1	CAPE TOWN	0	0	0	-	0	0	0	-	0	0	0	-	1	0	1	0.33
XIV 2	JOHANNESBURG	2	1	3	0.27	1	0	1	0.09	1	2	3	0.27	0	2	2	0.18
XIV 3	PRETORIA	1	0	1	0.10	2	0	2	0.20	0	1	1	0.10	0	0	0	-
XV	MADRID	1	2	3	0.15	2	1	3	0.15	0	1	1	0.05	1	0	1	0.51
XVI 1	LJUBLJANA	0	1	1	0.11	0	1	1	0.11	0	1	1	0.11	0	0	0	-
XVI 2	ZAGREB	1	0	1	0.12	2	0	2	0.24	1	0	1	0.12	1	1	2	0.24
	TOTAL	27	18	45	0.11	47	25	72	0.17	20	16	36	0.09	26	15	41	0.10

TABLE 7.2

TRACHEO-OESOPHAGEAL FISTULA AND OESOPHAGEAL STENOSIS IN SINGLE BIRTHS, OCCURRING WITH OTHER MALFORMATIONS IN THE N GROUP

Centre	No. in N group	Sex and survival	Consanguinity	Malformations
Melbourne 1	N 13	M SB	None	Tracheo-oesophageal fistula; IVSD; imperforate anus; renal agenesis; pulmonary hypoplasia; split foot (L); polydactyly radial (R)
Melbourne 1	N 7	M LBA	None	Tracheo-oesophageal fistula; CP
Melbourne 1	N 8	M LBA	FC	Tracheo-oesophageal fistula; imperforate anus; absent radii
Bombay	N 19	M LBA	None	Tracheo-oesophageal fistula; recto-urethral fistula
Bombay	N 22	M LBD	None	Tracheo-oesophageal fistula (Ladd type III); dysgenesis pelvis; abnormal leg (R)
Mexico 1	N 24	M LBD	None	Aplasia oesophagus and trachea; CP; polydactyly; abnormal ear
Belfast	N 7	M LBD	NR	Oesophageal atresia; imperforate anus
Hong Kong	N 3	M LBA	None	Oesophageal atresia; imperforate anus
Mexico 1	N 20	M LBA	None	Atresia of oesophagus (Ladd type I); atresia of anus; hemivertreba (D11); malformation of ribs
Melbourne 1	N 11	F SB	None	Tracheo-oesophageal fistula; IVSD
Singapore	N 6	F SB	None	Tracheo-oesophageal fistula; horseshoe kidney
Melbourne 1	N 9	F SB	None	Tracheo-oesophageal fistula; diaphragm defect (L)
Mexico 1	N 33	F LBA	None	Tracheo-oesophageal fistula; talipes (B)
Manila	N 29	F LBD	None	Tracheo-oesophageal fistula; imperforate anus (recto-vaginal fistula); brachycephaly; low-set ears; syndactyly
Johannesburg	N 6	F LBD	None	Tracheo-oesophageal fusion; IVSD; horseshoe kidney

TABLE 7.3

ANAL ATRESIA, ETC. IN SINGLE BIRTHS, OCCURRING WITH OTHER MALFORMATIONS IN THE N GROUP

Centre	No. in N group	Sex and survival	Consanguinity	Malformations
Bogotá	N 7	M LBD	None	Atresia rectum; recto-perineal fistula; microtia
Alexandria	N 5	M SB	None	Imperforate anus; polycystic kidneys
Czechoslovakia	N 21	M SB	None	Anal atresia; perineal fistula; pseudohermaphrodite; syndactylous toes
Hong Kong	N 1	M SB	None	Imperforate anus; small cystic kidneys
Hong Kong	N 2	M LBA	None	Imperforate anus; polydactyly (radial)
Bombay	N 4	M LBA	FC	Imperforate anus; HL/CP
Bombay	N 12	M LBA	None	Imperforate anus; paralysis of legs
Kuala Lumpur	N 2	M LBA	None	Imperforate anus; absence of thumb (R)
Kuala Lumpur	N 7	M LBD	None	Imperforate anus; absent ear (L)
Singapore	N 11	M LBA	None	Imperforate anus; rudimentary scrotum
Mexico 1	N 1	M LBA	None	Imperforate anus; bifid scrotum
Mexico 1	N 9	M LBA	None	Imperforate anus; talipes
Mexico 1	N 13	M LBD	None	Imperforate anus; malformed ears; talipes; dislocation of hips
Mexico 1	N 14	M LBA	None	Imperforate anus; hypoplasia of ears; talipes; micrognathia
Mexico 1	N 22	M LBA	None	Imperforate anus; hydrocoele; low-set ears
Mexico 1	N 34	M LBA	None	Imperforate anus; CHD; scoliosis
Mexico 2	N 3	M LBD	None	Atresia of anus; talipes; microphthalmia
Johannesburg	N 17	M LBD	None	Imperforate anus; cystic kidney (R); absent kidney (L); absent 4th rib (L); polydactyly (radial); IASD; abnormal lung lobulation
Zagreb	N 3	M LBA	None	Imperforate anus; malformed ears
Czechoslovakia	N 16	F LBD	None	Rectal fistula; IVSD; duodenal atresia
Singapore	N 2	F LBA	None	Imperforate anus; CP
Panama	N 5	F LBA	None	Imperforate anus; atresia of urinary meatus; hypogastric tumour
Manila	N 27	F LBA	None	Imperforate anus; low-set ears; phocomelia; hypertelorism; micrognathia
Ljubljana	N 10	F LBD	None	Anal atresia; CP; polydactyly (NFS)
Singapore	N 5	F LBA	None	Recto-vaginal fistula; talipes
Bogotá	N 10	? LBD	None	Imperforate anus (agenesis of genitalia); talipes; joint laxity
Bombay	N 18	? LBD	None	Imperforate anus; pseudohermaphrodite; aplasia of humerus (L)
Singapore	N 10	? LBD	None	Imperforate anus; hermaphrodite; malformed sternum

TABLE 7.4

EXOMPHALOS IN SINGLE BIRTHS, OCCURRING WITH OTHER MALFORMATIONS IN THE N GROUP

Centre	No. in N group	Sex and survival	Consanguinity	Malformations
Czechoslovakia	N 8	M LBA	None	Exomphalos; IVSD; patent foramen ovale
Czechoslovakia	N 9	M LBD	None	Exomphalos; hydroureter; hypospadias; microphthalmia
Czechoslovakia	N 20	M SB	None	Exomphalos; HL/CP; IVSD; chondrodystrophy
Bombay	N 1	M SB	None	Exomphalos; talipes; ectopia cordis
Kuala Lumpur	N 6	M LBD	None	Exomphalos; HL/CP (L)
Mexico 1	N 16	M LBA	None	Exomphalos; abnormal ears; abnormalities of limbs
Mexico 1	N 26	M LBA	None	Exomphalos; hypoplasia of genitalia; imperforate anus
Manila	N 12	M LBD	None	Exomphalos; microglossia
Johannesburg	N 3	M SB	None	Exomphalos; hypospadias
Johannesburg	N 7	M SB	None	Exomphalos; talipes; deformed hands
Johannesburg	N 10	M SB	None	Exomphalos; missing fingers and toes
Johannesburg	N 16	M LBD	None	Exomphalos; talipes; syndactyly; arm fused to body
Madrid	N 8	M LBD	None	Exomphalos; aplasia of genitalia; aplasia of kidneys; CHD
Melbourne 2	N 1	F LBD	None	Exomphalos; bicornuate uterus; IVSD; right-sided aorta; malformation of brain
Santiago	N 2	F LBD	None	Exomphalos; agenesis of genitalia; imperforate anus
Medellín	N 11	F LBD	None	Exomphalos; polydactyly (NFS); exocardia
Medellín	N 18	F LBA	None	Exomphalos; imperforate anus
Czechoslovakia	N 12	F LBD	None	Exomphalos; arcuate uterus; CP; fissured tongue
Kuala Lumpur	N 5	F LBD	None	Exomphalos; talipes; polydactyly (NFS); microcephalus
Belfast	N 18	F SB	NR	Exomphalos; microcephalus
Panama	N 12	F LBA	None	Exomphalos; persistent cloaca
Manila	N 18	F LBD	None	Exomphalos; aplasia of genitalia; missing fingers and toes
Medellín	N 12	? SB	FC	Exomphalos; ambiguous genitalia; HL
Hong Kong	N 14	? LBD	None	Exomphalos; undifferentiated genitalia
Bombay	N 2	? SB	None	Exomphalos; agenesis of genitalia